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09/709,045	11/10/2000	M. Rigdon Lentz	LEN 102	3239

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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/709,045	Applicant(s) LENTZ, M. RIGDON	
	Examiner Jegatheesan Seharaseyon	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,7 & 11* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-10, drawn to a method for inducing an immune response against transformed, infected or diseased tissue in Paper No.: 10 (7/29/02) is acknowledged. Applicant has elected to cancel claims 12-16 after amending claim 11. Therefore, claims 1-11 are pending.

2. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is

accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231. **Applicant claims priority to a provisional application by stating that priority information in the specification (page 1, line: 10). Please include this information along with the other priority information added in Paper No: 10. Correction is required.**

Specification

3. The disclosure is objected to because of the following informalities:

3a. The Applicant is addressing TNFR-1 and TNFR-2 in the specification and the claims both as tissue necrosis factor receptor and tumor necrosis factor receptor. However, the art recognizes TNFR receptors to be tumor necrosis factor receptors. Appropriate correction is required.

3b. On page: 1, line 23, thrombopoetin has to be followed by a (,) before granulocyte stimulating factor.

3c. On page: 6, line 4, TNFR receptor is abbreviated incorrectly.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Regarding claims 1 and 11, the acronyms " GM-CSF, G-CSF, M-CSF and SCF" render the claims vague and indefinite. Abbreviations and acronyms should be spelled out at their first use in the claims for clarity. Claims 2-10 are rejected insofar as they depend on rejected claim 1.

4b. Claims 1 and 11 are rejected as being vague and indefinite in the recitation of the term "molecule binding to soluble cytokine receptor molecules". It is unclear what molecules are contemplated for binding. Therefore, the metes and bounds of the claim are unclear. Claims 2-10 are rejected insofar as they depend on rejected claim 1.

4c. Claim 1 recites the limitation "the cytokine" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim. Rewriting the claims with "the cytokine receptor" can obviate this rejection. Claims 2-10 are rejected insofar as they depend on rejected claim 1.

4d. Claim 11 recites the limitation "the cytokine" in line 3. There is insufficient antecedent basis for this limitation in the claim. Rewriting the claims with "the cytokine receptor" can obviate this rejection.

4e.The "reduced in amount" in claim 1 and 11 is a relative term that renders the claims indefinite. In addition, it is not clear what is reduced and relative to what etc. It is not clear what the Applicant implies when reciting "..until the transformed, infected, or diseased tissue is reduced in amount." It is also unclear what the transformed, infected and diseased tissues are and how they are affected. Claims 2-10 are rejected insofar as they depend on rejected claim 1.

4f. Claim 7 recites the limitation "the soluble cytokine receptor molecules are selected from the group consisting of soluble tissue necrosis factor receptor-1 ("sTNFR-1") and soluble tissue necrosis factor receptor-2 ("sTNFR-2") ". There is insufficient antecedent basis for this limitation in the claim. Claims 8 and 9 are rejected insofar as they depend on rejected claim 7.

4g. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: it is unclear how the reduction in transformed, infected, or diseased tissue will induce an immune response. Claims 2-10 are rejected insofar as they depend on rejected claim 1.

Claim Rejections - 35 USC § 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 1, 4, 6, 8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification recites the removal of TNF receptor by blocking the binding of TNF to TNF receptor ("TNF-Rs"). Specifically, the specification teaches the use of molecules that bind to the soluble TNF receptor for its removal from blood (page 3). The specification also recites use of restorative agents like GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF, to restore platelet and white cell levels (page 1). However, the specification does not disclose cytokines that are selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF that can induce the immune response against transformed, infected or diseased tissue upon the binding of a molecule preventing the soluble cytokine receptor from binding to the said cytokine. The claims as written, however, encompass cytokine molecules or soluble receptors which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 1-11. The specification does not provide written description for all sulphamates. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is*

now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

With the exception of the removal of soluble TNF receptor by blocking the binding of TNF to TNF receptor, the skilled artisan cannot envision the detailed structure of the claimed cytokine molecules and the respective soluble cytokine receptors, regardless of the complexity or simplicity of the method of identifying cytokine molecules and the cytokine receptors. As a result, it does not appear that the inventors were in possession of invention to use the cytokine molecules or the soluble cytokine receptors set forth in claims 1, 4, 6, 8 and 11. Claims 2, 3, 5, 7, 9 and 10 are rejected insofar as they depend on rejected claim 1.

5b. Claims 1, 4, 6, 8 and 11 rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Applicant intends to use selective removal or neutralization of the soluble cytokine receptors (which function as inhibitors of the cytokine) to promote a selective, safe inflammatory response against a tumor and viral or parasitic diseases (page 5-6). The role of TNF in the immunomodulation is well documented. The art of record also teaches the inhibitory effect of TNFRI receptor on TNF. However, it is unclear what role GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF play in inducing an immune response. The art and specification also teach the use of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF to restore platelet and white cell levels. Thus, it would appear that inhibiting the binding of these cytokines to its receptors would not be desirable out come in terms of treating tumors or infections. In addition, it is unclear if GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF all have soluble receptors that can be selectively removed.

Applicant uses a single *in vivo* experiment to illustrate the reduction of solubilized receptors to tumor necrosis factor. In this experiment the Applicant uses anti sTNF-R1 monoclonal antibody and anti sTNF-R2 monoclonal antibody to remove the receptor. Subsequent to the receptor removal Applicant asserts that there was no melanoma and

there was considerable reduction in the vertebral body lesion in the patient (pages: 14-20). Based on these results, Applicant contends that the removal of soluble TNF receptors offers considerable therapeutic advantage for the treatment of tumors. The *in vivo* experiment on a single patient without any controls is less than convincing with respect to the effect of sTNF receptors. This combined with the lack of teaching in the art for other soluble cytokine receptor molecules and the lack of guidance provided in the specification, will not allow one of skill in the art to practice the invention without undue experimentation.

Given the breadth of claims 1, 4, 6, 8 and 11 in light of the unpredictability of the art as determined by the working examples and the prior art of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention to induce an immune response against transformed, infected or diseased tissue and prevent the soluble cytokine receptor from binding to the cytokine, until the transformed, infected, or diseased tissue is reduced in amount. Claims 2, 3, 5, 7, 9 and 10 are rejected insofar as they depend on rejected claim 1.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6a. Claims 1, 2 and 6-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-8 of U.S. Patent No. 6,231,536.

The instant invention is directed to inducing an immune response against transformed, infected or diseased tissue and prevents the soluble cytokine receptor from binding to the cytokine, until the transformed, infected, or diseased tissue is reduced in amount. U.S. Patent No. 6,231,536 teaches methods and compositions for treating cancers. Specifically, the method uses ultrapheresis to remove soluble cytokine receptors to stimulate the patient's immune system to attack solid tumors (abstract). The broad claims generically read on the instant invention, though the patent does not explicitly recite the removal of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF soluble cytokine receptors to induce immune response.

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method described in the patent to remove other soluble cytokine receptor molecules to induce an immune response. One skilled in the art, at the time the invention was made to would have been motivated to substitute molecules which will bind other soluble cytokine receptor molecules to enhance the immune response. Thus, claims 1, 2 and 6-9 of the instant application are obvious over claims 1, 2 and 5-8 of U.S. Patent No. 6,231,536. Claims 3, 4, 5, 10 and 11 are rejected insofar as they depend on rejected claim 1.

7. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph. D, whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JEFFREY STUCKER
PRIMARY EXAMINER